

An Emerging Role of mTOR in Lipid Biosynthesis Minireview

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Lipid biosynthesis is essential for the maintenance of cellular homeostasis. The lipids produced by cells (glycerolipids, fatty acids, phospholipids, cholesterol, and sphingolipids) are used as an energy source/reserve, as building blocks for membrane biosynthesis, as precursor molecules for the synthesis of various cellular products, and as signaling molecules. Defects in lipid synthesis or processing contribute to the development of many diseases, including obesity, insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease, and cancer. Studies published over the last few years have shown that the target of rapamycin (TOR), a conserved serine/threonine kinase with an important role in regulating cell growth, controls lipid biosynthesis through various mechanisms. Here, we review these findings and briefly discuss their potential relevance for human health and disease.

Introduction

The mammalian TOR (mTOR) protein is a serine/threonine kinase belonging to the phosphoinositide 3-kinase (PI3K)-related kinase family that has an important role in regulating cell growth and metabolism. As depicted in [Figure 1](#), mTOR nucleates at least two distinct multi-protein complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (reviewed in [\[1\]](#)). mTORC1 is composed of mTOR, regulatory-associated protein of mTOR (Raptor), mammalian lethal with Sec13 protein 8 (mLST8, also known as GβL), proline-rich Akt substrate 40kDa (PRAS40), and DEP-domain-containing mTOR-interacting protein (Deptor). This complex integrates four major signals — growth factors, energy status, oxygen, and amino acids — to regulate many processes involved in the control of cell growth and metabolism. mTORC2, which is composed of mTOR, rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase interacting protein (mSin1), protein observed with Rictor-1 (Protor-1), mLST8, and Deptor, is activated by growth factors and regulates cell survival, cell metabolism, and cytoskeletal organization (reviewed in [\[2\]](#)).

From yeast to mammals, favorable conditions, such as nutrient and oxygen availability, induce cell growth by activating the TOR pathway. For many years, regulation of cell growth by mTOR has been studied mostly in relation to protein synthesis, the best-characterized biological output controlled by this pathway. However, it is becoming increasingly clear that mTOR also controls cell growth by promoting the activation of other anabolic processes, leading to the

synthesis of many classes of lipids (unsaturated and saturated fatty acids, phosphatidylcholine, phosphatidylglycerol, and sphingolipids) that are required for membrane biosynthesis and energy storage. Here, we review these findings, focusing on what has been learnt about mTORC1 effectors in lipid synthesis and about a possible role for mTORC2 in lipogenesis from studies of lower organisms. We also discuss the potential relevance of these recent findings for the treatment of human diseases, including cancer, obesity, and non-alcoholic fatty liver disease (NAFLD).

mTORC1-Mediated Control of Lipogenesis through SREBP-1

When total energy intake exceeds energy expenditure, excess carbohydrates are converted to fatty acids and deposited for storage as triglycerides in hepatic and adipose tissue. This process, defined as *de novo* lipogenesis, is strongly driven by insulin (reviewed in [\[3\]](#)). The binding of insulin to its cell surface receptor activates PI3K, promotes the production of phosphatidylinositol (3,4,5)-triphosphate (PIP₃), and increases the recruitment and the activation of Akt at the plasma membrane (reviewed in [\[4\]](#)). When activated, Akt positively regulates *de novo* lipogenesis by promoting glucose uptake, glycolysis, and the expression of genes involved in lipid biosynthesis (reviewed in [\[5\]](#)). Many lines of evidence suggest that Akt mediates the effect of insulin on *de novo* lipogenesis by activating the transcription factor sterol regulatory element-binding protein-1 (SREBP-1) (reviewed in [\[6\]](#)).

SREBPs are basic helix–loop–helix transcription factors that regulate lipid homeostasis by controlling the expression of genes required for cholesterol, fatty acid, triglyceride, and phospholipid synthesis. Three members of the SREBP family have been described in mammals: SREBP-1a and -1c, which are produced by alternative splicing; and SREBP-2, which is encoded by another gene. SREBP-1c and -2 are considered the most physiologically relevant because of their high expression in lipogenic tissues (reviewed in [\[7\]](#)). SREBPs are synthesized in the endoplasmic reticulum (ER) in the form of a precursor protein. In order to reach the nucleus and act as a transcription factor, the amino-terminal domain of each SREBP must be released from the ER proteolytically. SREBP-1 and -2 are cleaved and activated in response to different signals: SREBP-2 is activated in response to cellular sterol depletion, whereas SREBP-1c, which is insensitive to sterol levels, is activated by insulin (reviewed in [\[7\]](#)). Accordingly, studies using genetically engineered mouse models show that SREBP-2 mainly controls cholesterol biosynthesis, whereas SREBP-1c is involved in insulin-mediated fatty acid synthesis (reviewed in [\[6\]](#)).

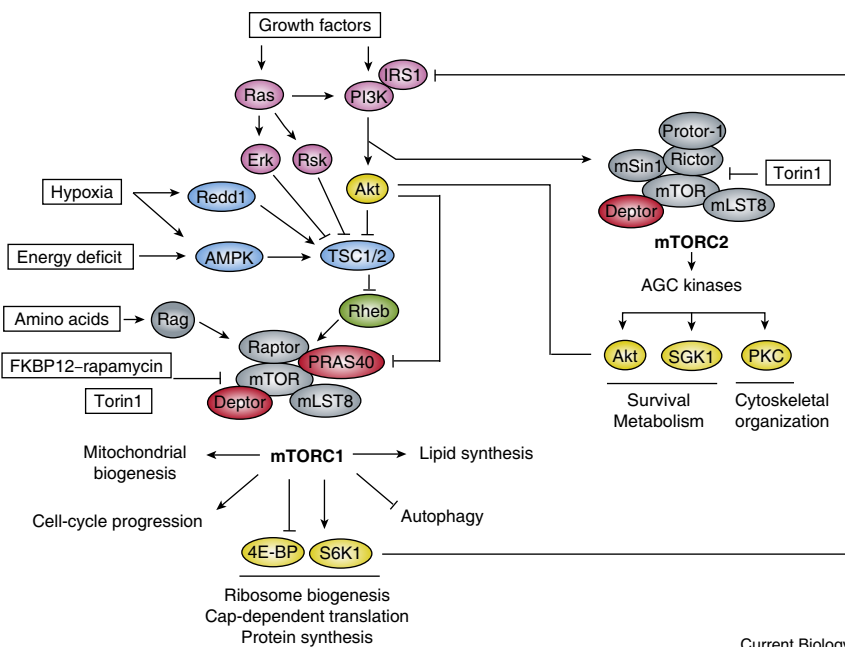
Insulin treatment or constitutive Akt activation rapidly induces nuclear accumulation of SREBP-1 and the expression of lipogenic genes [\[8,9\]](#). The precise mechanism by which insulin signaling promotes SREBP-1 cleavage has remained elusive for many years. As shown in [Figures 1 and 2](#), growth factors such as insulin increase Akt activity, which in turn promotes mTORC1 activation by directly phosphorylating tuberous sclerosis complex 1/2 (TSC1/2) and PRAS40. Porstmann *et al.* [\[10\]](#) observed that inhibition of

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Figure 1. Overview of the mTOR signaling pathway.

The mTOR kinase nucleates two characterized protein complexes termed mTORC1 and mTORC2. mTORC1 is composed of five subunits: the mTOR catalytic subunit, Raptor, mLST8, PRAS40, and Deptor. The mTORC2 complex contains six proteins: mTOR, Rictor, mSin1, Protor-1, mLST8, and Deptor. mTORC1 is sensitive to nutrients and is inhibited by FKBP12-rapamycin. One of the most important sensors involved in the regulation of mTORC1 activity is TSC, which is a heterodimer composed of TSC1 and TSC2. TSC1/2 functions as a GTPase-activating protein for the small, Ras-related GTPase, Rheb. The active, GTP-bound form of Rheb directly interacts with mTORC1 to stimulate its activity. As a Rheb-specific GAP, TSC1/2 negatively regulates mTORC1 signaling by converting Rheb into its inactive GDP-bound state. Stimulation of cells with growth factors activates Akt, extracellular signal-regulated kinase (Erk), and ribosomal S6 kinase (Rsk), which inactivates TSC and promotes Rheb activation. Akt activation also promotes mTORC1 activity by phosphorylating PRAS40, a negative regulator of mTORC1. Induction of Redd1 and AMPK by hypoxia and energy deficit activates TSC1/2 and downregulates mTORC1 signaling. The activation of mTORC1 by amino acids is regulated by the Rag GTPase and is independent of TSC1/2. Activation of mTORC1 by growth factors or amino acids promotes protein synthesis via the phosphorylation of S6K1 and 4E-BPs. High activation of S6K1 by mTORC1 induces a feedback inhibition loop in which S6K1 reduces growth factor signaling by promoting the phosphorylation and the degradation of IRS-1. mTORC2 is activated by growth factors and regulates many AGC kinases (Akt, SGK1, protein kinase C (PKC) α) that have key roles in controlling cell survival, metabolism and cytoskeletal organization. This complex is insensitive to FKBP12-rapamycin but is inhibited by the newly characterized mTOR inhibitor Torin1. FKBP12, intracellular receptor for rapamycin; IRS-1, insulin receptor substrate-1; Redd1, transcriptional regulation of DNA damage response-1; Rheb, Ras homolog enriched in brain.



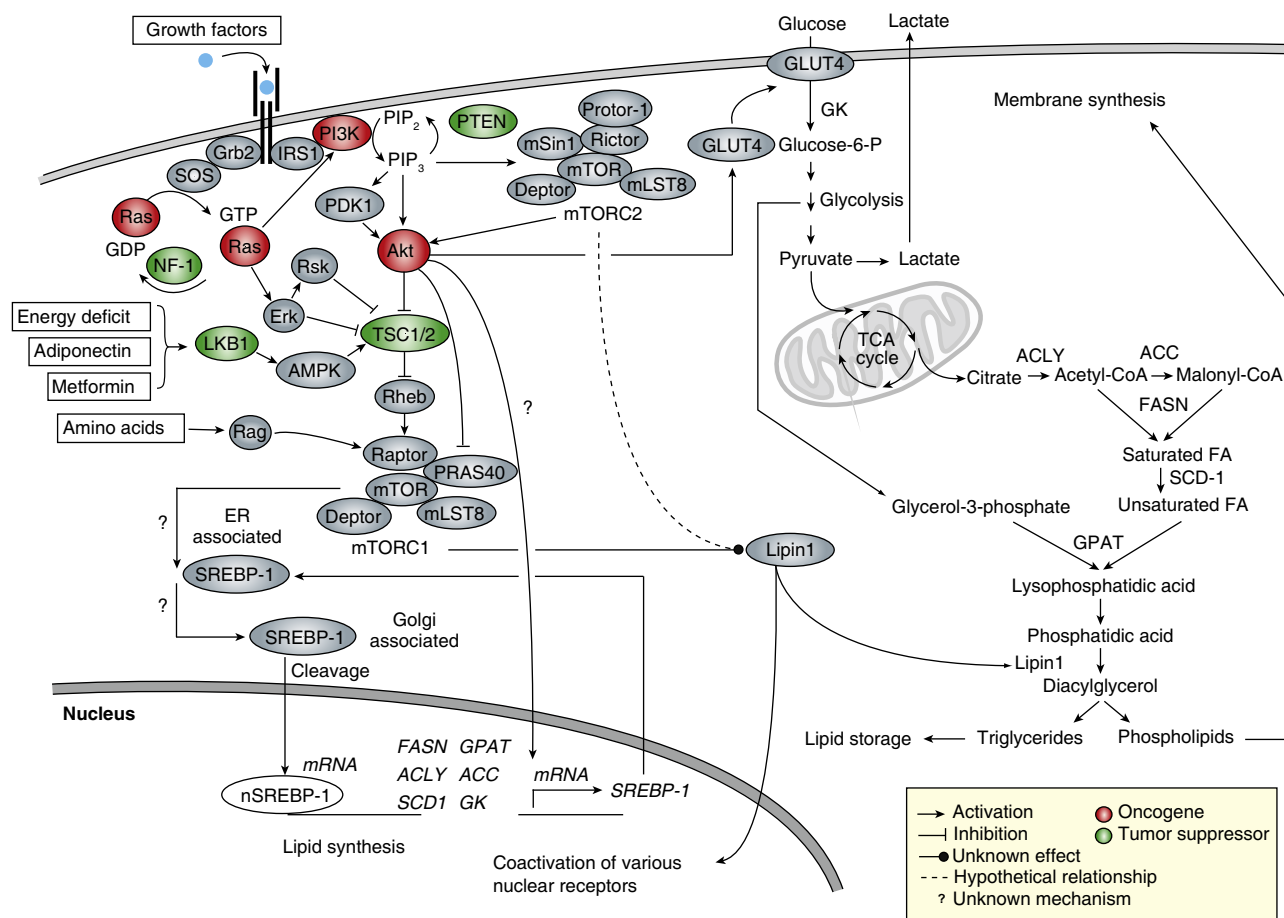
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mTORC1 with rapamycin blocks Akt-induced SREBP-1 nuclear localization, the expression of lipogenic genes, and the production of various classes of lipids (unsaturated and saturated fatty acids, phosphatidylcholine, and phosphatidylglycerol). The knockdown of Raptor, but not Rictor, showed similar effects, indicating that SREBP-1 activation by Akt depends on mTORC1 but not mTORC2. This finding supports previous work that showed that rapamycin reduces the expression of many SREBP-1 target genes, including acetyl-CoA carboxylase (ACC) [11], fatty acid synthase (FASN) [12], and stearoyl-CoA desaturase 1 (SCD-1) [13]. In addition to establishing a link between mTORC1 and SREBP-1, Porstmann *et al.* [10] nicely demonstrated that SREBP-1 depletion restricts mammalian cell growth and fly size, suggesting that the PI3K-Akt-mTORC1 pathway regulates cell size by promoting both protein and lipid biosynthesis. The exact mechanism by which mTORC1 promotes SREBP-1 cleavage and nuclear localization remains to be determined.

Increased *de novo* lipid synthesis is a hallmark of proliferating cancer cells (reviewed in [14]). Uncontrolled growth factor signaling caused by the mutation/amplification of genes encoding proteins involved in PI3K and Ras signaling is commonly observed in tumors and serves as a key signaling event leading to the activation of SREBP-1 and *de novo* lipogenesis (Figure 2). A significant body of evidence suggests that the induction of lipid biosynthesis through the activation of SREBP-1 facilitates cancer progression by providing the lipids required for membrane synthesis (reviewed in [14]). The observation that mTORC1 promotes SREBP-1 activation indicates that this protein complex may play a central role in cancer cell growth/proliferation by relaying growth factor signals to lipid synthesis (Figure 2).

These results strongly suggest that mTORC1 inhibition with rapamycin, or with the newly characterized mTOR inhibitors [15–17], may reduce cancer cell growth/proliferation by blocking both protein and lipid biosynthesis. Further investigations are needed to support this hypothesis.

NAFLD, a condition produced by fat accumulation in the liver, is the most common liver disease and can eventually lead to non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinomas (reviewed in [18]). NAFLD is commonly observed in obese subjects and is closely linked to insulin resistance and metabolic syndrome, a combination of medical disorders that increase the risk of developing cardiovascular diseases and type 2 diabetes. A recent study performed in obese humans revealed an important role of *de novo* lipogenesis in the excessive accumulation of hepatic triglycerides [19]. Although highly dependent on insulin for its activation, lipogenesis is paradoxically very active in the liver of obese rodents, which are characterized by severe hepatic insulin resistance. Interestingly, mTORC1 is also highly active in the liver of obese rodents [20]. In addition to reducing insulin signaling by promoting insulin receptor substrate-1 (IRS-1) phosphorylation or degradation (Figure 1), mTORC1 hyperactivation by overfeeding may promote lipogenesis by inducing SREBP-1c cleavage and activation. The nutrient-dependent activation of mTORC1 may explain why hepatic SREBP-1c is highly activated even in the context of profound liver insulin resistance. Additionally, it is interesting to note that metformin, an antidiabetic drug known to activate AMP-activated protein kinase (AMPK), reduces hepatic lipid content by promoting fatty acid oxidation and by impairing SREBP-1c expression and cleavage [21]. Because AMPK negatively regulates mTORC1



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Figure 2. mTORC1 promotes *de novo* lipogenesis through the activation of SREBP-1.

The activation of mTORC1 in response to growth factors induces many anabolic processes that favor cell growth and proliferation. In addition to promoting protein synthesis through the phosphorylation of S6K1 and 4E-BPs, mTORC1 controls *de novo* lipid synthesis by regulating the activation state of SREBP-1. In detail, growth factors activate Akt, Erk and Rsk, which induce TSC1/2 phosphorylation and lead to mTORC1 activation. Akt also directly promotes mTORC1 action through the phosphorylation of PRAS40. When activated, mTORC1 favors the cleavage of SREBP-1 by a mechanism that remains to be established. The cleaved form of SREBP-1 then translocates to the nucleus where it induces the expression of many lipogenic genes, including acetyl-CoA carboxylase (ACC), acyl-CoA lyase (ACLY), fatty acid synthase (FASN), glycerol-3-phosphate acyltransferase (GPAT), glucokinase (GK) and stearoyl-CoA desaturase-1 (SCD-1). These proteins catalyze numerous enzymatic processes that are essential for the synthesis of fatty acids, triglycerides, and phospholipids. Mutations in tumor suppressors or oncogenes that lead to the overactivation of Ras and insulin signaling pathways are commonly observed in cancer and are thought to promote cell growth and proliferation by inducing many anabolic processes, including lipid biosynthesis. The induction of lipogenesis through the activation of SREBP-1 promotes cancer progression by providing the lipids required for membrane synthesis. The fact that mTORC1 promotes SREBP-1 activation indicates that this protein complex may play a central role in cancer cell growth/proliferation by relaying growth factor signals to lipid synthesis. FA, fatty acid; Grb2, growth factor receptor bound protein 2; NF-1, neurofibromatosis type 1; PDK1, phosphoinositide-dependent kinase 1; PTEN, phosphatase and tensin homologue deleted on chromosome 10; SOS, son of sevenless; nSREBP-1, nuclear form of sterol regulatory element-binding protein-1; TCA cycle, tricarboxylic acid cycle.

(Figures 1 and 2), this suggests that AMPK activators (metformin, adiponectin) may reduce fat deposition in the liver by affecting the expression of lipogenic genes through an mTORC1–SREBP-1c-dependent mechanism. The involvement of the mTORC1–SREBP-1c axis for the control of lipid synthesis in the other important lipogenic tissue, i.e. adipose tissue, will be discussed in the next section.

mTORC1-Mediated Control of Lipogenesis through PPAR- γ and Lipin1

Adipogenesis is the biological process leading to the formation of mature adipocytes from adipose cell precursors. This process follows a well-orchestrated program in which

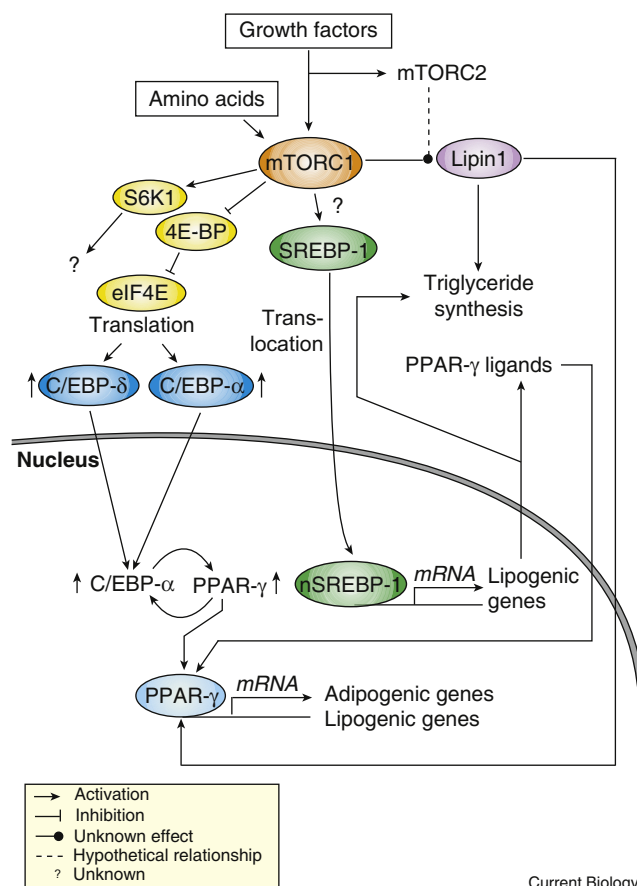
CCAAT/enhancer binding protein- β (C/EBP- β) and C/EBP- δ trigger the expression of C/EBP- α , which in turn induces the expression of peroxisome proliferator-activated receptor- γ (PPAR- γ), a member of the nuclear receptor superfamily of ligand-activated transcription factors (reviewed in [22]). The activation of PPAR- γ leads to profound changes in gene expression that ultimately lead to the stimulation of fatty acid uptake, synthesis, esterification, and storage in the newly formed adipose cell.

Rapamycin strongly inhibits the adipogenic program in mouse and human pre-adipocytes *in vitro* [23–29]. It was initially shown that rapamycin blocks adipogenesis by impairing the clonal expansion of pre-adipocytes [29], an

early event thought to be required for the establishment of the normal adipogenic program *in vitro* (reviewed in [22]). Over the following years, it was found that rapamycin severely reduces lipid accumulation in fat cells even when added after clonal expansion, indicating that mTORC1 affects adipogenesis and adipocyte maintenance through additional mechanisms [23,24,26,28]. Most of the studies linking mTOR signaling to adipogenesis were based on long-term rapamycin treatments, an experimental condition that can also lead to mTORC2 inhibition [30]. To determine the specific role of mTORC1 in adipogenesis and adipocyte maintenance, Polak *et al.* [28] knocked down Raptor in 3T3-L1 adipocytes and observed a reduction in adipogenesis. Additionally, it was recently shown that adipose-specific deletion of Rictor does not affect adipocyte size and adipose tissue mass *in vivo* [31]. Although it remains to be determined if acute knockdown of Rictor leads to similar effects, these observations strongly suggest that mTORC1, but not mTORC2, plays a key role in adipogenesis in mammalian cells.

Although the exact mechanism linking mTORC1 signaling to adipogenesis and adipocyte maintenance is unknown, observations suggest that mTORC1 may control these processes by regulating the expression and the activation state of PPAR- γ (Figure 3). Many independent groups have reported that rapamycin-mediated mTOR inhibition reduces mRNA and protein levels of PPAR- γ and C/EBP- α and the expression of numerous lipogenic genes *in vitro* [23,24,26]. Accordingly, constitutive activation of mTORC1 via loss of TSC2 increases PPAR- γ and C/EBP- α expression and promotes adipogenesis [32]. Some evidence indicates that eukaryotic initiation factor 4E-binding proteins 1 and 2 (4E-BP1 and 2), negative regulators of translation that are inhibited by mTORC1, are important for the regulation of PPAR- γ and C/EBPs by mTORC1 [27,33]. Disruption of 4E-BP1/2 promotes the expression of PPAR- γ , C/EBP- α , and C/EBP- δ and increases adipogenesis/lipid synthesis in mouse embryonic fibroblasts [33]. Although the activation of p70 ribosomal S6 kinase 1 (S6K1), and probably other mTORC1 substrates, is induced by the deletion of 4E-BP1/2 [33], these results suggest that mTORC1 controls adipogenesis/lipogenesis by inducing the translation of mRNA encoding key components of the adipogenic program, namely PPAR- γ and C/EBP- α . Additionally, the observation that S6K1-deficient mice have reduced adipose tissue mass and are protected against diet-induced obesity indicates that mTORC1 may also control adipogenesis/lipogenesis through this effector [34]. The molecular mechanism by which S6K1 may control lipid metabolism is unknown.

It is interesting to note that mTORC1 may also regulate adipogenesis through additional and complementary mechanisms. As discussed in the previous section, mTORC1 promotes lipid synthesis by increasing SREBP-1 cleavage and activation [10]. SREBP-1 activation triggers the production of endogenous ligands for PPAR- γ and this promotes the transactivation activity of this nuclear receptor [35]. Interestingly, Kim *et al.* [24] observed that the synthetic PPAR- γ ligand troglitazone can overcome the inhibitory effect of rapamycin on adipogenesis, suggesting that mTORC1 inhibition may block adipogenesis by reducing the production of endogenous PPAR- γ ligands. However, it is possible that troglitazone, as an unnatural ligand, may override the normal requirements for PPAR- γ activation and thus counter rapamycin inhibition unspecifically. The fact that conditioned



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Figure 3. mTORC1 promotes adipogenesis and adipocyte maintenance through various mechanisms.

Much evidence indicates that mTORC1 controls adipogenesis by activating PPAR- γ , a nuclear receptor controlling the expression of numerous genes involved in fatty acid uptake, synthesis, esterification, and storage. Many mechanisms are thought to be involved in the regulation of PPAR- γ by mTORC1. Activation of mTORC1 induces the phosphorylation of 4E-BPs, which in turn releases eIF4E and increases the translation of C/EBP- α and - δ , which are key components required for the establishment of the adipogenic cascade. C/EBP- δ is known to drive the expression of C/EBP- α and PPAR- γ and to trigger the activation of a feed-forward loop in which these two transcription factors reciprocally induce their expression. When sufficient levels of PPAR- γ proteins are produced, this transcription factor promotes adipogenesis and lipid synthesis by inducing the expression of many lipogenic genes. SREBP-1 cleavage by mTORC1 may also contribute to the induction of adipogenesis by directly favoring triglyceride synthesis and by promoting the production of endogenous ligands for PPAR- γ . More work is required to determine whether SREBP-1-dependent production of PPAR- γ ligands plays a significant role in the activation of PPAR- γ by mTORC1. Lipin1, a phosphatidic acid phosphatase, was shown to play a key role in adipogenesis by promoting triglyceride synthesis and by serving as a coactivator for PPAR- γ . Lipin1 is phosphorylated in response to insulin and amino acids in a rapamycin-sensitive fashion. Because rapamycin can inhibit mTORC2 activity in some cell types, it is unclear whether lipin1 is a direct substrate of mTORC1 or mTORC2. The biological significance of mTOR-mediated lipin1 phosphorylation remains to be characterized.

media obtained from normally differentiated adipocytes cannot correct the adipogenic defect of adipocytes treated with rapamycin indicates that this possibility may be true [24]. Additional work is needed to clarify this point.

Lipin1 is a phosphatidic acid phosphatase that promotes triglyceride synthesis by converting phosphatidic acid to

diacylglycerol. A null mutation in the lipin1 gene leads to lipodystrophy, whereas lipin1 overexpression causes obesity (reviewed in [36]). In addition to directly promoting triglyceride synthesis through its phosphatidic acid phosphatase activity, lipin1 acts as a transcriptional coactivator for many transcription factors, including PPAR- γ . Lipin1 physically interacts with PPAR- γ to induce the expression of many genes playing key roles in adipogenesis [37]. Accordingly, studies with lipin1-null embryonic fibroblasts revealed that lipin1 is required for the expression of key adipogenic markers, such as PPAR- γ and C/EBP- α , and for the attainment of mature adipocyte functions, including lipogenesis and lipid accumulation [38]. As a consequence, lipin1 is thought to affect adipogenesis and adipocyte maintenance by directly promoting triglyceride synthesis and amplifying the transcriptional activity of PPAR- γ . Lipin1 activity is regulated by many mechanisms, including phosphorylation. In adipocytes, lipin1 is phosphorylated in response to insulin and amino acids in a rapamycin-sensitive fashion, thus suggesting that mTOR signaling may directly regulate adipogenesis/lipogenesis through the control of lipin1 activity [39]. More work is needed to characterize the biological link between mTOR and lipin1, because the exact consequences of lipin1 phosphorylation on lipid synthesis and gene expression have not been characterized so far.

As described throughout this section, the link between mTORC1 and PPAR- γ in the control of adipogenesis and adipocyte maintenance has been well established *in vitro*. In order to determine the role of mTORC1 in adipocytes *in vivo*, Polak *et al.* [28] specifically ablated Raptor in adipose tissue after the critical steps required for the induction of adipogenesis, thereby focusing on the role of mTORC1 in adipocyte maintenance. In line with the *in vitro* studies, Raptor deletion in fat results in lean mice with a reduction in adipocyte size and number. Unexpectedly, the expression of many genes involved in lipid production and storage, including PPAR- γ and C/EBP- α , is not reduced in adipose tissue of these animals. Polak *et al.* [28] observed that mTORC1 inactivation reduces fat accumulation in adipose tissue by promoting energy expenditure through an induction of uncoupled respiration. Interestingly, a similar increase in energy expenditure is observed in many animal models deficient for proteins that play key roles in lipogenesis [40–42]. This raises the possibility that the reduction in fat mass and the induction of energy expenditure in adipose-specific Raptor-null animals could be linked to a defect in lipogenesis that is likely independent of PPAR- γ -induced lipogenic gene expression. The potential implication of lipin1 or SREBP-1 in this effect has to be considered.

Obesity, defined as an excess amount of body fat relative to lean body mass, is a major health concern in the United States and an increasing problem in the developing world. Recent advances regarding the biology of adipose tissue have demonstrated that the white adipose tissue plays a central role in the control of energy balance and acts as a powerful endocrine organ that mediates numerous physiological and pathological processes (reviewed in [43]). It was observed that mTORC1 is highly active in the adipose tissue of obese rodents [34]. The existence of a link between mTORC1 activation and adipogenesis/lipogenesis suggests that mTORC1 may play a significant role in the accumulation of fat when energy intake exceeds energy expenditure. Understanding the role of mTORC1 signaling in the development and the maintenance of adipose tissue and in the

control of its endocrine function may promote the development of new pharmacological tools to treat metabolic diseases associated with obesity, such as insulin resistance, type 2 diabetes and coronary vascular diseases.

Implication of mTORC2 in Lipid Biosynthesis

Two recent reports indicate that impairment of TORC2 function affects fat accumulation in *Caenorhabditis elegans* [44,45]. Despite developmental delay and reduced body size, Rictor-null worms show increased body fat accumulation, thus suggesting that TORC2 functions as a negative regulator of lipid deposition in this model. Jones *et al.* [44] found that the induction of lipid storage in Rictor-null *C. elegans* depends on the TORC2 substrate serum- and glucocorticoid-induced protein kinase 1 (SGK1) but not Akt, as only SGK1 loss can mimic the metabolic phenotype associated with Rictor deletion. The precise mechanism linking the TORC2–SGK1 axis to lipid metabolism was not described in this study. In the other report, Soukas *et al.* [45] observed that the high-fat phenotype associated with Rictor loss is associated with a reduction in oxygen consumption and is dependent on SGK1, but also Akt1 and Akt2. Soukas *et al.* also show that the site of action of Rictor in the regulation of fat mass is the intestine, which is the key site for fat storage in *C. elegans*. Although the conclusions drawn in these reports do not perfectly match, these studies demonstrate that TORC2 plays a significant role in regulating fat accumulation in *C. elegans* and that SGK1 is required in this process. An interesting question arising from these observations is whether or not a similar link between mTORC2 and lipid synthesis exists in mammalian cells. The fact that adipose-specific Rictor-null mice [31] and mice lacking SGK isoforms throughout all tissues (reviewed in [46]) do not show any defect in lipid metabolism suggests that mTORC2 may have a more subtle role to play in the control of lipid metabolism in mammals. Whether or not this is a consequence of the higher genetic redundancy of mammalian systems remains to be determined.

Although the implication of mTORC2 in the control of lipogenesis/adipogenesis appears to be limited in mammals, recent observations in yeast suggest that this complex may regulate other facets of lipid metabolism. Aranava *et al.* [47] recently showed that the synthesis of minor and major ceramide species is impaired in yeast cells deficient in TORC2 activity. In the same report, it was observed that TORC2 controls *de novo* sphingolipid synthesis by regulating the activity of ceramide synthase through a mechanism dependent on Ypk2, the yeast homologue of SGK1. Although the exact mechanism linking Ypk2 to ceramide synthase has not been characterized, these results indicate that TORC2 plays a role in transmitting growth signals to sphingolipid synthesis in yeast. Because the early steps in *de novo* sphingolipid synthesis are well conserved throughout evolution (reviewed in [48]), it is reasonable to believe that mTORC2 could control this pathway in mammals. Sphingolipids, which include sphingosine and ceramides, have been implicated in a variety of physiological functions, including differentiation, cell migration and adhesion, cell growth arrest, senescence and apoptosis. These lipids are believed to play important roles in many pathological settings, such as cancer, heart disease, diabetes, microbial infection, neurological disorders and immune dysfunctions. The possible implication of mTORC2 in the regulation of ceramide levels indicates that mTORC2 may play important and yet

undefined roles in these diseases and may also represent an interesting target for the development of new therapeutic avenues. Additional studies are required to determine whether mTORC2 plays a significant role in controlling *de novo* sphingolipid synthesis in mammalian cells.

Concluding Remarks

Lipid biosynthesis is essential for the maintenance of cellular homeostasis and defects in lipid synthesis or processing contribute to the development of many diseases, including obesity, insulin resistance, type 2 diabetes, NAFLD, and cancer. Over the last decade, many groups have shown that mTOR signaling regulates lipid synthesis through various effectors, suggesting that this pathway could be targeted for the development of new therapeutic tools for the treatment of many diseases. Despite outstanding advances, our understanding of the mechanisms by which mTOR signaling affects lipid synthesis in mammals is incomplete and important questions remain to be answered. For example, how does mTORC1 promote SREBP-1 cleavage and nuclear localization? What is the exact mechanism by which mTORC1 regulates the activity of PPAR- γ ? How does mTORC1 control lipid synthesis in adipose tissue *in vivo*? What is the biological function associated with lipin1 phosphorylation by mTOR? What is the exact role of mTORC2 in the regulation of lipogenesis? Does mTORC2 regulate sphingolipid synthesis in mammals? Finding answers to these questions will improve our understanding of cell biology and may help to improve the way we treat many diseases.

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